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Letter to the Editor

Academicians Are More Likely to Share Each Other's Toothbrush Than Each Other's Nomenclature [Cohen, 1982]

To the Editor:

Recently Botto et al. [1996] presented a case-control study in this journal, covering a total of 13 cases of limb deficiencies divided into 2 populations after chorionic villus sampling (CVS), namely the US Multistate CVS study and the Italian Multicentric Birth Defects study (IPMC). They pointed out that differences in results of various studies on this issue might be a consequence of different classification systems for limb defects. Classification and terminology of limb deficiencies is a crucial point in the discussion of a possible relationship between limb defects and first trimester prenatal diagnosis by CVS. Solving this communication difficulty might indeed help us get a step further in this ongoing and sometimes unproductive controversy.

Important differences in the use of terminology were mentioned by Froster and Jackson [1994] at the ASHG meeting in relation to the US Multistate CVS study, to which Botto et al. [1996] refer in their paper. Being directly addressed and realizing that the essential differences in classification systems were again missed by the authors [Botto et al., 1996] prompted me to delineate these differences in various classification systems which are presently in use for the description of congenital limb deficiencies, including the classification system we had used for analysing limb defect cases in British Columbia [Froster-Iskenius and Baird, 1992] and in the WHO-CVS study [Froster and Jackson, 1996].

It might be important to emphasize that I do not claim that the system we use is any better than any other system for the classification of limb defects, but we had used this system consistently for the 2 large studies mentioned above and we think that if data from other authors are compared to data from our studies, there is a need for consistency in the use of definitions.

Classification of Congenital Limb Defects

There is agreement that "reduction" defects of the limbs are understood as defects in which skeletal parts of the limbs are lacking. Reviewing the larger studies on this issue for the last 10 years [Aro, 1982; Bod et al., 1983; Källen et al., 1984; Froster-Iskenius and Baird, 1989, 1992; Lenz and Majewski, 1991; Stoll et al., 1992, 1994; Evans et al., 1994; Castilla et al., 1995], there are considerable differences in ordering limb defects, one of the central points being classifying sites of defects versus cases with pattern of deficiencies.

All recent classification systems are based on the suggestions of Frantz and O'Rahilly [1961] who used anatomical descriptions. These classifications were designed to help the orthopaedists designate the various deficiencies accurately. The main distinction was between terminal and intercalary defects, which could be either transverse or longitudinal. They used terms such as amelia, hemimelia, acheiria and apodia, adactyly and aphalangia, or phocomelia. Extensive illustrations in their paper helped associate the clinical picture with the descriptive term. The descriptive terms, such as phocomelia, hemimelia and so on were eliminated by several working groups from the orthopaedic point of view [Committees of the American Society for Surgery of the Hand, International Federation of Societies for Surgery of the Hand] and substituted by anatomical terms [Burtch, 1974; Swanson, 1976; Entin, 1977]. In these latter anatomical classification systems, the multitude of clinical terms was reduced to two main descriptive terms: Amelia for complete absence of one or more limb and meromelia for partial absence of a limb. There were further subdivisions into categories such as: terminal deficiencies, intercalary deficiencies, transverse, longitudinal, preaxial, postaxial, central and rudimentary. As these were classification systems meant for the use of orthopedic surgeons, anatomical descriptions were used and care was taken that the system allowed for details of the deficient bones. Even though defects of the lower limbs were also classified, the focus was on classification of the upper limbs.

The morphological classification aimed at a potential therapeutic approach and thus, descriptions included all parts of the limbs which were still present. For reconstructing the function of the deficient limb, this description is important. However, researchers with a view on pattern of anomalies and syndromes are primarily interested in the overall diagnosis. A very de-

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tailed description of deficiencies might distract attention from the actual diagnosis. Temtamy and McKusick [1978] classified anomalies of the hand into 6 main categories: (1) terminal transverse defects, (a) ectrodactyly, adactylia, acheiria, (b) amelia and terminal transverse hemimelia, (c) acheiropody; (2) radial defects; (3) ulnar defects; (4) radioulnar defects; (5) phocomelia; and (6) split-hand/split-foot anomaly, (a) typical split hand, (b) atypical split hand, reintroducing the terms hemimelia, acheiropody and phocomelia, which had been eliminated by the anatomically oriented classification systems [Burtch, 1976]. There also is potential overlap in the categories terminal transverse defects and radioulnar defects.

The problem of describing sites of defects rather than a pattern of anomalies was addressed by Lenz and Majewski [1991], who distinguish 6 groups of limb deficiencies: brachydactyly, syndactyly, polydactyly, oligodactyly, peromelia and synostoses. In their outline on classifications of limb defects they express concern that a strictly morphological approach to a limb defect classification might disrupt groups of defects, such as the femur-fibula-ulna-complex or Poland anomaly.

Population based and epidemiological studies of limb deficiencies from various Malformation Registries do not always have access to roentgenograms and precise anatomical descriptions of cases. Thus, in such studies there is a need to find a practical system which allows counting defects of the limbs in a reproduceable way. However, there has not been much agreement on the classification systems used: starting with the early study of Birch-Jensen [1949], who distinguished 11 categories: split-hand, atypical split hand, ectrodactylism, radial defects, ulnar defects, radio-ulnar defects, "amputation" of upper arm, "amputation" of forearm, "amputation" of hand, symbrachydactylism, exogenous "deformities." Aro et al. [1982] distinguished between 2 main categories: terminal and intercalary defects and then between longitudinal, pre- and postaxial or ulnar-fibular defects, transverse defects, as a defect covering entirely or partly pre- and postaxial parts, split-hand/split-foot and phocomelia. Bod et al. [1983] separate 5 groups: terminal transverse, longitudinal preaxial: radial, tibial, longitudinal postaxial: ulnar-fibular, central axis:split-hand and/or foot, ring constrictions. Källén et al. [1984] identify 18 groups of limb defects: (1) sirenomelia; (2) amelia; (3) phocomelia; (4) micromelia (5) amputations; (6) "reduction" of humerus; (7) "reduction" of radius; (8) "reduction" of ulna; (9) "reduction" of femur; (10) "reduction" of tibia; (11) "reduction" of fibula; (12) absence or hypoplasia of thumb; (13) radial hand reduction; (14) ulnar hand reduction; (15) other hand reduction; (16) tibial foot reduction; (17) fibular foot reduction; (18) other foot reduction).

At this point, Froster-Iskenius and Baird [1989] had started to undertake the British Columbia study on limb defects. Reviewing available classification systems, we found that all of them classified single defects rather than cases. In particular, the classifications chosen by the orthopaedic surgeons were aimed at therapy and thus, described all parts present with the view of a possible reconstruction or functional reconstruction of remaining parts. However, they were too detailed for diagnostic purposes and a genetic point of view. Besides a precise description we were interested in recognizing new combinations or pattern of limb deficiencies. We found that a considerable number of infants born with congenital defects of the limbs had more than one bone involved and in fact did show a pattern of limb anomalies and not just a single defect. Thus, we needed a classification that allowed a genetic-diagnostic approach. Thus, we decided to base our classification on the recommendations of Burtch [1976] and Swanson [1977], but instead of counting single bone defects, we introduced a hierarchy approximating a developmental time table of limb development [Froster-Iskenius and Baird, 1992], which would avoid disruption of defect patterns. According to previous studies we used two main categories: amelia for the complete absence of one or more limbs and meromelia for partial absence of parts of a limb. The categories are mutually exclusive, as described in (Table I), so that each case will only be counted once, by the bone that is still present. For example, if an infant has a defect of the radius and some toes, it will only appear in the group of radius defects and the deficiencies in other bones will be mentioned in the description of the case, but do not count. As there are fewer cases having multiple defects of bone structures, this approach does not disrupt groups and is also applicable for variable combinations of limb deficiencies.

The heterogeneity in classification of limb deficiencies remains and is expanding in studies published during the last 5 years [Evans et al., 1994; Castilla et al., 1995; Stoll et al., 1992, 1994]. It resulted in further variations of limb classifications: Stoll uses 5 categories: (1) terminal transverse defects; (2) proximal-intercalary defects; (3) longitudinal defects; (4) split hand/foot; (5) multiple types of reduction defects. The last category applies to 36 to 123 cases, i.e., 29%. Evans et al. [1994] distinguish 11 different groups of defects: (1) amelia; (2) rudimentary limb; (3) terminal transverse; (4) longitudinal preaxial; (5) longitudinal postaxial; (6) intercalary; (7) split hand/foot; (8) digital deficiencies; (9) other; (10) mixed; and (11) insufficient information. Castilla et al. [1995] separate 25 different groups of limb defects, including amelia, 4 types of amputations, 3 types of hypoplasias, 2 types of phocomelias, 2 types of preaxial and 2 types of postaxial defects, axial defects, and 7 types of combined defects. The problem with all these systems is that there remain considerable numbers (8–33% of cases) of combined defects (Table II), which cannot be classified, if the classification system allows only for sites of deficiency.

Looking at the differences in classification of limb defects, it appears almost impossible to find two studies matching in all criteria. One main difference is that some authors use sites of defects, while others use cases and yet others use a mixture of both and it is also not always clear whether the separate categories are mutually exclusive. For the purpose of this statement, it would go too far to expand on differences in defining the

TABLE I. Classification and Coding System for Limb Deficiencies

Group of defect	Includes	Excludes	Type of defect
I. Amelia	II.		Transverse
II. Meromelia upper limb	IIA–K and III	I	
IIA Humerus defect	IIB–K and III	I	Transverse
IIB Ulnar defect	IIC–K and III	I,IIA	Longitudinal
IIC Radius defect	IID–K and III	I–IIB	Longitudinal
IID Radial/ulnar defect	IIE–K and III	I–IIC	Transverse
IIE Hand	IIF–K and III	I–IID	Transverse
IIF Digits, preaxial	IIG–K and III	I–IIE	Longitudinal
IIG Digits, postaxial	IIH–K and III	I–IIF	Longitudinal
IIH Digits, middle (ectrodactyly, split hand)	IIK–K and III	I–IIK	Longitudinal
IIK Digits, unspecified	III	I–IIK	Longitudinal
III. Meromelia lower limb	IIIA–H	I and II	
IIIA Femur defect	IIIA–H	I and II	Transverse
IIIB Fibular defect	IIIB–H	I,II,IIIA	Longitudinal
IIIC Tibia defect	IIIC–H	I,II,IIIA,B	Longitudinal
IIID Fibular/tibial defect	IIID–H	I,II,IIIA–C	Transverse
IIIE Foot defect	IIIE–H	I,II,IIIA–D	Transverse
IIIF Toes, preaxial	IIIF–H	I,II,IIIA–E	Longitudinal
IIIG Toes, postaxial (ectrodactyly, split foot)	IIIG–H	I,II,IIIA–F	Longitudinal
IIIH Toes, unspecified	IIIH	I,II,IIIA–G	Longitudinal

single categories; however, it has to be at least mentioned that even a simple term like transverse defect has different meanings in different studies.

Botto et al. [1996] have used the EUROCAT classification system [Stoll et al., 1992, 1994], which uses sites of deficiency rather than cases. Therefore, the category of transverse defects is different from the one we use in 2 respects: first a transverse defect of the hand or the fingers would in our definition mean all fingers including the thumb or all toes, respectively, if defects of the digits or toes are looked at. They have appreciated this differences in their groups TDD-4 and TDD-5. Second, we use cases, rather than sites of defects; thus, our category of transverse defects could apply to different levels of defects. We differentiate between a "hypoplasia of the hand and arm" plus defects of single digits, which would of course be a transverse defect, but it would be in a different category than a transverse defect of the hand or a transverse defect of the foot. Now, the 13 cases listed in the study would, according to the classification we use [Froster-Iskenius and Baird, 1992, Froster and Jackson, 1996] be listed in several different groups (cases 1, 10, 11, 13: IIIE; case 2: IIF; case 3: IIK; case 4: IIIG; cases 5,6: IIH; cases 7,9: IIG; case 8: IID; case 12:IIE). Nevertheless, it is interesting to note that those cases which were classified as transverse defects. (TDD-5), in agreement with our terminology, occur with the same frequency (two cases each) regardless whether CVS took place at the 8th or 10th week of gestation. With so few cases (4 and 9 cases in each category, respectively) split over 11 gestational weeks, we would suggest caution before drawing definitive conclusions or recommendations towards a potential danger of CVS.

TABLE II. Percentage of Unclassified Mixed or Multiple Limb Defects in Various Studies

Study	Total	Mixed type	% of total
Evans et al. [1994]	275	26	9.45
Stoll et al. [1992]	123	36	29.2
Stoll et al. [1994]	49	4	8.2
Aro et al. [1983]	402	49	12.2
Källen et al. [1984]	1,046	352	33.6

Limb deficiencies as possible indicators for environmental hazards or exogenous disturbances of fetal development are important. Therefore, it would be desirable to discuss this subject in a more efficient way than is presently done. One way might be to have a consensus meeting on terminology of limb defects for epidemiological and genetic studies in the near future. We would suggest to have such a meeting which would clearly help communication in this complicated but important field.

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